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1 **Potential immuno-nanomedicine strategies to fight COVID-19 like pulmonary infections**

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20

21 **Abstract**

22 COVID-19, coronavirus disease 2019, caused by the severe acute respiratory syndrome  
23 coronavirus 2 (SARS-CoV-2) has become a pandemic. At the time of writing this (October 14,  
24 2020), more than 38.4 million people have become affected, and 1.0 million people have died  
25 across the world. The death rate is undoubtedly correlated with the cytokine storm and other  
26 pathological pulmonary characteristics, as a result of which the lungs cannot provide sufficient  
27 oxygen to the body's vital organs. While diversified drugs have been tested as a first line therapy,  
28 the complexity of fatal cases has not been reduced so far, and the world is looking for a treatment  
29 to combat the virus. However, to date, and despite such promise, we have received very limited  
30 information about the potential of nanomedicine to fight against COVID-19 or as an adjunct  
31 therapy in the treatment regimen. Over the past two decades, various therapeutic strategies,  
32 including direct-acting antiviral drugs, immunomodulators, a few non-specific drugs (simple to  
33 complex), have been explored to treat Acute Respiratory Distress Syndrome (ARDS), Severe  
34 Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS),  
35 influenza, and sometimes the common flu, thus, correlating and developing specific drugs centric  
36 to COVID-19 is possible. This review article focuses on the pulmonary pathology caused by  
37 SARS-CoV-2 and other viral pathogens, highlighting possible nanomedicine therapeutic  
38 strategies that should be further tested immediately.

39

40 **Keywords:** Coronavirus; COVID-19; influenza, pulmonary drug delivery; SARS, SARS-CoV-2;  
41 MERS, nanomedicine; nanotherapeutics, pathophysiology

42

## 43 **Introduction**

44 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiological  
45 source to cause Coronavirus Disease 2019, or COVID-19. Around 80% of cases of COVID-19  
46 will be mild to moderate, close to 14% have severe disease and around 6% are critical. The  
47 possible symptoms include fever, headache, muscle pain, fatigue, and breath shortness followed  
48 by the multi-organ failure. Nearly 20% of COVID-19 patients are experiencing Acute  
49 Respiratory Distress Syndrome (ARDS) [1,2]. The high mortality rates depend on several  
50 clinical factors, such as ARDS, pneumonia, sepsis-induced by the ‘cytokine storm’ (e.g., an  
51 uncontrolled release of cytokines which causes systemic inflammation) followed by lung failure,  
52 coagulopathy and thrombotic events, secondary bacterial infections, and vital organ  
53 (heart/liver/kidney) injuries followed by failure, and others [1,3-5]. Thus, considering the surge  
54 in the new cases and death rate, the World Health Organization announced COVID-19 as a  
55 pandemic [6]. The origin of the COVID-19 first arose in the Wuhan, China on December 16,  
56 2019. Later, its genome was likely correlated with the bat's genome, nearly 96% similar;  
57 assuming that it has been transferred from animals, e.g., bats and pangolins (zoonotic disease)  
58 [7,8].

59 SARS-CoV-2 infects both humans and animals, and it has been globally infecting  
60 humans **with more than 38.4 million cases and more than 1,091,605 deaths (as per October 14,**  
61 **2020)**, which is far greater than the SARS and Middle East Respiratory Syndrome (MERS). The  
62 infection is spreading through human-human and animal-human transmission via oral-oral and  
63 oral-faecal route [9]. Recently, the Advisory Committee on Dangerous Pathogens (ACDP) in the  
64 UK categorized the SARS-CoV-2 as a hazard group 3 organism.

65 Like other SARS-CoV, SARS-CoV-2 also uses angiotensin 1-converting enzyme 2  
66 (ACE2; a close homologue of ACE) for entry into the cells [10,11], in addition to ACE2, it also  
67 uses the other cellular protease including transmembrane protease serine 2 (TMPRSS2) [12,13],  
68 which is useful in priming of the process of SARS-CoV-2. Recently, one study concluded that  
69 SARS-CoV preferentially infects well-differentiated ciliated epithelial cells expressing ACE2.  
70 Since ACE2 is also the receptor for the coronavirus NL63, their findings are relevant to the  
71 biology of infection with this more common human pathogen [14]. Among other tissues, high  
72 expression of ACE2 is found in the lungs and the small intestine [15]. For the SARS-CoV  
73 infection, expression of ACE2 in the airway epithelia appears to be both necessary and essential.

74 The airway epithelial expression ACE2 is complex and correlated with cell differentiation, a  
75 finding that may underlie susceptibility to infection [14]; thus, a probable source for the viral  
76 loads. Besides, the recent single-cell transcriptome data on *ACE2* and *TMPRSS2* revealed that  
77 nasal epithelial cells (goblet/secretory cells and ciliated cells) exhibit high *ACE2* gene expression  
78 when compared to other epithelial cells [16]. Equally important, alveolar type II cells exhibit a  
79 high expression of *ACE2*. Besides, there is a concern for other associated receptors that act  
80 synergistically with infections, i.e., viral scavenging (DMBT1) receptors [17]. On the other hand,  
81 high expression of furin, which exposes the binding and fusion domains of SARS-CoV-2, has  
82 also been observed in oral epithelial cells [18]. Interestingly, considering the human-human  
83 transmission through sneezing and coughing, it is clear that SARS-CoV-2 infects epithelial cells  
84 in the upper airway epithelium [16], later the alveoli (type II cells) [19], and oral mucosa [20].

85 Despite the recent developments in clinical modalities for multiple pulmonary infections,  
86 there is an unmet medical need for developing more effective targeted nano-delivery systems.  
87 This site-specific local delivery of nano-engineered therapeutic agents with controlled release  
88 and stabilization of the therapeutic agent play a crucial role in the management of COVID-19  
89 like pulmonary infections. The foremost challenges with traditional pulmonary drug delivery  
90 include lack of penetrability, non-targeted systemic delivery, and interaction with multiple  
91 targets at a single therapeutic site. Any advancements in pulmonary nano-drug delivery systems  
92 aim to provide maximum therapeutic efficacy with minimal off-targeted side effects, ease of  
93 functionalization (chemically, biologically), personalized therapy which together has  
94 concomitant benefits. In addition to the potential therapeutic abilities, nanotechnology plays an  
95 essential role in bringing cost-effective, quick nano-diagnostics tools to detect pulmonary  
96 infection associated biomarkers.

97 With current approaches to avoid infection and the realization that transmission is the  
98 only possible intervention that can be implemented along with complementary medicine and  
99 support care, no feasible COVID-19 regimen is available. However, to counter the ongoing  
100 outbreaks of COVID-19, a vast number of medications (previously licensed and new drug  
101 candidates) targeting various stages of the virus cycle and host immune cells have been  
102 considered [21]. In this current review, we discuss the inflammatory response (cytokine storm) in  
103 SARS-CoV2 infection, particularly in the lungs. In addition, we also highlight the currently  
104 repurposing of drugs and immunotherapeutic targets against COVID-19. Finally, we have placed

105 a perspective towards nanomedicine by considering the previous investigations ensued in the  
106 field of COVID-like infectious diseases.

### 107 **Inflammatory responses of COVID-19 and lung pathology**

108 The majority of the COVID-19 symptoms and pathological features, at least to some  
109 degree, have also been observed in SARS and MERS infections [2,22-24], which also come  
110 under the category of zoonotic diseases [25].

111 A macroscopic examination of COVID-19 post-mortem suggests pleurisy, pericarditis,  
112 lung contraction, and pulmonary oedema. [22]. There are also reports suggesting increased lung  
113 weight. Computed tomography (CT) scans are considered as the best diagnostic method for  
114 COVID-19 infections [26]. The CT scan report of COVID-19 patients showed bilateral lung  
115 opacities/infiltrates and hypoxemia with peripheral involvement of lower lobes [22]. Gross  
116 pathological observations clearly showed diffuse alveolar damage specifically air sac/alveolar  
117 tissue becoming more thickened and scarred permanently due to extensive fibrinogen deposition  
118 and associated fibrotic changes (elevated of D-dimer) in the extracellular matrix leading to  
119 shortening of breath, pulmonary hypertension and heart failure. Also, numerous pulmonary  
120 micro/macrothrombi have been observed, which are repressed by the use of heparin [27,28] and  
121 tissue plasminogen activator [29]. These complex reasons cause the lungs to lose their  
122 mechanical-stretchable properties, followed by interstitial fibrosis, bronchoconstriction, and  
123 other symptoms [2].

124 Dysfunction of the lungs can be characterized by the shortness of breath, which might be  
125 due to several reasons, including lungs occupied with a high amount of interstitial fluid, high  
126 content accumulation of collagen, not being able to produce enough surfactant, etc. These typical  
127 properties affect the lung tissue elasticity and affects gas transport (pulmonary circulation and  
128 diffusion of gas) functions. Lung histology showed the existence of damaged epithelial and  
129 endothelial cells, accumulation of exudates, red-blood cells, granulocytes (neutrophils), innate  
130 immune cells (monocytes, macrophages, dendritic cells), and lymphocytes (T helper and  
131 cytotoxic T cells) in the alveolar spaces that lead to a reduction in gas exchange function. Due to  
132 the inflammatory conditions, the rate of diffusion of gas across the alveoli alters, which leads to a  
133 hypoventilation condition in the lungs. During a poor gas exchange state, cells experience a high  
134 level of stress, which leads to apoptosis and/or necrosis. The role of neutrophils, such as the  
135 release of neutrophil elastases, chemokine receptors (CXCR2), and others, on lung epithelial cell

136 apoptosis, has been documented in the literature [30]. In addition to neutrophil chemokines, type  
137 II epithelial cells also express several chemokines in response to the infection [31].

138 In general, during the infections, the lung epithelium protects the host by providing  
139 coordinated innate and adaptive immune responses [32] (**Box 1**). The lung epithelium maintains  
140 the dry airspace by regulating the movement of proteins and fluids in and out of the lung.  
141 However, in acute infection conditions, like COVID-19, the activation of innate immune cells  
142 cross their threshold limit, which results in massive pro-inflammatory cytokine (IL-1 $\beta$ , IL-6, and  
143 tumor necrosis factor [TNF]- $\alpha$ ) production followed by propagation as severe systemic  
144 inflammation. Alveolar macrophages and monocyte-derived macrophages are the primary source  
145 for the pro-inflammatory cytokines, especially in SARS, MERS, and ARDS. In addition to  
146 alveolar macrophages, type II epithelial cells also produce large amounts of pro-inflammatory  
147 cytokines [33,34]. The recurrent inflammatory cascades in the lungs further damage epithelial  
148 and endothelial membranes followed by air sac tissue matrix damage. In addition, accumulation  
149 of cytokines, chemokines, and reactive oxygen species-rich fluid damage the complete alveoli  
150 structure and function, resulting in a low level of oxygen supply to the blood. In this condition,  
151 intensive care unit (ICU) patients are supported by artificial air ventilators. Although the use of  
152 ventilators is the only option for severely affected COVID-19 patients, it has long been known  
153 that the continuous use of ventilation induces lung injury via alveoli cell apoptosis, i.e.,  
154 ventilator-induced/associated lung injury [35]. Therefore, it is essential to use possible adjunct  
155 therapies to overcome treatment-induced injuries.

156

### 157 **Cytokine storm in COVID-19**

158 SARS-CoV-2 interacts and induces alveoli tight epithelial cell barrier damage followed  
159 by lung injury, which is considered as the primary injury. In addition, infection triggers the  
160 further damage of the tight junctions, production of reactive oxygen species and activates innate  
161 immune cells (e.g., macrophages) which worsen the condition. This type of immune cell  
162 activation induced damage is termed as the secondary injury, i.e., the inflammatory injury.  
163 Regardless of the direct primary injury, secondary injury is widely implicated in many other  
164 pathogenic infections, including but not limited to influenza, SARS, MERS, and others [24].

165 Upon infection (including SARS and MERS), the internalized virus uses host  
166 intracellular machinery to propagate while destroying host cells. In result, host cells deliver

167 danger signals, i.e., IL-6 and TNF- $\alpha$ . The danger signals recruit the innate immune cells to attack  
168 the virus. However, due to the presence of unseen viral signals, the innate immune system  
169 delivers copious amounts of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , interferon [IFN]-  
170  $\gamma$ , and others), i.e., called the cytokine storm (**Fig. 2**), which induces non-selective immunogenic  
171 cell death followed by organ failure. The above process has been recurrently observed in the  
172 lungs of SARS-CoV-2-infected patients, especially patients in the ICU [36]. Hyper activated  
173 lymphocytes are the additional culprits in causing the cytokine storm. Patients with severely ill  
174 COVID-19 infection show the existence of hyperactivated CD4<sup>+</sup> and CD8<sup>+</sup> CD38<sup>+</sup>HLA-DR<sup>+</sup> T-  
175 cells. In vitro stimulation of COVID-19 patients' peripheral blood mononuclear cells with a pool  
176 of peptides (resembling SARS-CoV-2 proteome) revealed the existence of SARS-CoV-2-  
177 specific CD4<sup>+</sup> and CD8<sup>+</sup> responses. Upon stimulation with peptides, CD4<sup>+</sup> and CD8<sup>+</sup> showed  
178 activation (CD69 and CD137) and memory (CD45RA<sup>-</sup> and CCR7<sup>+</sup>) responsive marker  
179 expression with predominantly Th1 biased cytokine secretion [37].

180 Due to the inflammatory storm that occurs in COVID-19 patients, the development of  
181 ARDS results. The initiation of ARDS starts with the recruitment of immature alveolar  
182 macrophages at the airspaces in the alveoli; under the influence of growth factors (e.g.,  
183 granulocyte-macrophage colony-stimulating factor (GM-CSF), cytokines, etc.) they differentiate  
184 into mature alveoli macrophages [38]. Upon maturation, they secrete chemotactic factors, such  
185 as IL-8 and other chemokines to attract other inflammatory immune cells [39]. However, each  
186 immune cell, e.g., neutrophils, macrophages, megakaryocytes [40], and others, have their own  
187 distinct role in infectious conditions. In addition, infection signals the recruitment of neutrophils  
188 to the edematous space, across the endothelium, interstitium, and epithelium, whereby they  
189 activate and perform regulatory functions, such as phagocytosis of pathogens. Comparably, an  
190 increased neutrophil count (i.e., neutrophilia) has been observed in the severely ill COVID-19  
191 patients and is accompanied by the severity of the disease [36].

192 Nevertheless, due to the inflammatory microenvironment, the hyperactivation of  
193 neutrophils leads to secondary damage to the alveoli. Mediators of neutrophil-induced lung  
194 injury include proteases (neutrophil elastase), oxidants (reactive oxygen and nitrogen species),  
195 antimicrobial peptides (defensins), and Neutrophil Extracellular Traps (NET). Indeed, the same  
196 progression was observed in other lung injury diseases (ARDS, MERS, SARS, and influenza)  
197 [30]. Therefore, strategies, which target hyperactivation of neutrophils or their inflammatory



198 mediators, such as CXCR2 (neutrophil chemokine receptor) antagonists, inhibition of neutrophil  
199 proteases, inhibitors of peptidylarginine deiminase IV, inhibitors of DNase-1, and others, would  
200 be beneficial for COVID-19 (reviewed elsewhere [30]).

201 In addition to neutrophils, macrophages have also been implicated in lung injury during  
202 pathogenic infections, e.g., influenza. Blocking monocyte-derived macrophage recruitment to the  
203 inflammatory site has attenuated secondary injury induced by macrophages [39,41]. More  
204 importantly, pro-inflammatory cytokines, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and others, have a  
205 significant role in both primary and secondary injuries. Interestingly, monocyte-derived  
206 macrophage releasing of TRAIL (TNF-related apoptosis-inducing ligand) is one of the causative  
207 factors for epithelial cell apoptosis; infected epithelial cells express surface death receptors. It  
208 has been reported that SARS-CoV-2-induced lung injury consequently degenerates the spleen  
209 and lymph nodes. Among the clinical abnormalities, lymphopenia, or lymphocytopenia, is a  
210 primary significant condition observed in COVID-19 patients. Recent tissue histopathological  
211 studies of the spleen and lymph nodes from COVID-19 patients revealed that macrophages,  
212 especially ACE2 expressing CD169<sup>+</sup> tissue-resident macrophages, are also directly infected by  
213 SARS-CoV-2. Probably, viruses envisage the capability of macrophages that deals with death  
214 [42]. However, unlike MERS-CoV [43], these viruses do not directly infect T and B cells [44].  
215 Upon infection, these macrophages produce pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ) and  
216 activate lymphocytes. Subsequently, IL-6 has been used, along with other markers, as a potential  
217 inflammatory biomarker in COVID-19 to assess the severity and to provide a prognosis [45].  
218 Historically, fatal cases of ARDS, influenza, MERS, and SARS are associated with IL-6 and IL-  
219 1 $\beta$  followed by macrophage-activation, and a similar trend has also been observed in COVID-19  
220 [46]. Consequently, the activated lymphocytes exhaust [47] and express a high content of Fas  
221 receptor, which mediates the Fas/FasL signaling and induces activation-induced cell death,  
222 causing lymphocytopenia [44].

223 In addition to neutrophil and macrophage induced secondary injuries, recruited dendritic  
224 cells, and antigen presentation to the cytotoxic CD8<sup>+</sup> T cells also accelerate the inflammatory  
225 process. Dendritic cells recruited to the inflammatory site access the virus and process the  
226 antigen presentation to CD8<sup>+</sup> T cells. Viral antigen-experienced CD8<sup>+</sup> T cells clear the viral load  
227 by killing the infected epithelial cells through the release of perforin/granzyme-mediated or the  
228 Fas ligand process.

229 In addition to the mentioned irregularities and inflammatory injuries, another factor that  
230 causes lung tissue injury is the hypoxia condition. Due to the edematous condition of the alveoli,  
231 epithelial cells are more vulnerable to apoptosis, which allows for impaired tissue integrity and  
232 their functions (e.g., gas exchange). Lung epithelial cell apoptosis is mediated by several  
233 pathways, including a Fas ligand pathway, toll-like receptor (TLR) pathways, intracellular stress-  
234 induced, and others [48].

235

### 236 **Current repurposed drugs and immunotherapeutic targets available against COVID-19**

237 Unfortunately, at present, there are no newly-developed approved drugs and vaccines for  
238 the treatment of COVID-19. However, knowing about the uncertainty of the efficacy of new  
239 drugs/vaccines and the lengthy discovery and developmental timeline, special efforts have been  
240 made to repurpose existing drugs including antiviral drugs, immunomodulators, and other  
241 adjunct therapies (**Fig. 2**) [49,50]. The proposed drugs and their existing targets may or may not  
242 work in a similar fashion with SARS-CoV-2. Nevertheless, detailed studies need to be conducted  
243 to confirm their possible mechanism of action.

244

### 245 **Virus attachment inhibitors**

246 In addition to structural homology, SARS-CoV and SARS-CoV-2 spike (S) proteins  
247 exhibit high similarity sequences (nearly 76.5%) [51,52], which preferentially bind to human  
248 ACE2 receptors. Earlier studies on SARS-CoVs have shown that overexpression of ACE2 and  
249 the injection of spike proteins exacerbated disease severity and lung injury, respectively. As  
250 mentioned-above, SARS-CoV-2 also uses ACE2 for its entry into cells [53]. Henceforward,  
251 strategies that hinder the virus-ACE2 interaction have been explored (**Table 1**), such as serine  
252 protease (TMPRSS2) inhibitors (camostat mesylate) [12], the use of monoclonal antibodies  
253 against ACE2, the use of recombinant ACE2 protein (APN01, GSK2586881), and drugs that act  
254 on the renin-angiotensin system [52]. Along a similar line, the S protein has gained much  
255 attention as a target to develop monoclonal antibodies [54].

256

### 257 **Virus entry/fusion inhibitors**

258 Although the spike protein in SARS-CoV and SARS-CoV-2 appears to be similar in  
259 homology, SARS-CoV-2 binds to different amino acids and shows high-affinity binding towards

260 human ACE2 receptors; glutamine residue (at 394 position) in the SARS-CoV-2 receptor-  
261 binding domain (RBD) interacts with the lysine (at 31 position) on the human ACE2 receptor  
262 [11,52,55]. On the other hand, SARS-CoV entry is facilitated by host cell proteases, such as  
263 elastase, cathepsin B, L and/or TMPRSS2. In addition to the proteases as mentioned above,  
264 SARS-CoV-2 exhibits a peculiar furin-like cleavage site, which is processed by the furin at the  
265 cell surface and trans-Golgi network (TGN) for entry and egress, respectively [18,56,57]. By  
266 using molecular modelling, diversified furin inhibitors have been proposed [57].

267

### 268 **Antiviral therapeutics for COVID-19**

269 A majority, but not all antiviral drugs come under the class of nucleoside analogues,  
270 which mimic the features of nucleic acid and disrupt the virus replication. A list of antiviral  
271 drugs tabulated here is explored in for many infections, even sometimes in human studies, such  
272 as HIV, influenza, hepatitis B (HBV), hepatitis C (HCV), and others. Several bioinformatic  
273 and/or *in vitro* studies on cells have been confirmed and proposed to use known antiviral drugs  
274 as anti-SARS-CoV-2 inhibitors (**Table 1**) [58-60].

275

### 276 **Immunomodulation for COVID-19**

277 Despite several reasons for mortality, mortality induced by the immune-compromised  
278 conditions is confessed, especially in the older age population (~60 years). Various  
279 immunoregulatory functions are altered in COVID-19 like pathologies and in addition, the  
280 cytokine storm incurs severe damage to the host tissue. Thus, modulation of COVID-19-  
281 associated immune responses is mandatory.

282

#### 283 *Immunostimulatory drugs*

284 A murine model of infection confirmed that CoVs modulate host immune responses by  
285 delaying type I interferon (IFN-I) to avoid the detection process [61], e.g., after infection, non-  
286 structural proteins (nsp; particularly nsp15) play a significant role in the inhibition of IFN-I  
287 responses, which is essential for the innate immune system to clear the virus-infected cells  
288 [62,63]. Interestingly, the highest similarity (95%) of this protein was observed in SARS-CoV-2  
289 as well with that of SARS-CoV [64], which raises the possibility to use novel approaches  
290 including TLR agonists, IFN agonists, and others (**Table 1**).

291 *Immunotherapies that target inflammatory cytokines or hyperactivated immune cells*

292 Antagonists to inflammatory mediators are widely used in autoimmune diseases in which  
293 hyperactivated immune cells damage different organs in the body. From the past few decades,  
294 the autoimmune disease associated therapeutic interventions are accompanied by the inhibition  
295 of cytokines, including TNF, IL-17A, IL-6, IL-23, and others or blockade their receptors like IL-  
296 6R [65,66]. Through this strategic targeting, the infiltration of monocytes, macrophages, and  
297 lymphocytes is regulated. Similarly, as explained earlier, COVID-19 infection also has shown  
298 hyperimmune activation; thus, the aforementioned strategies are useful as an adjunct therapy  
299 [67,68]. Several clinical studies identified that pro-inflammatory cytokines are the causative  
300 factors for the severe lung damage and coagulopathy observed in COVID-19 patients,  
301 particularly, predominant levels of IL-6 and TNF (**Table 1**) [4]. IL-6 and TNF- $\alpha$  antagonists  
302 have been used in the treatment of cytokine release syndrome. Thus, many clinical studies  
303 (**Table 1**) have been initiated with the same hypothesis.

304 Many other possible immunotherapeutic strategies (**Table 1**), such as passive  
305 immunotherapy to neutralize SARS-CoV-2, regulatory T cell-targeted therapies, cellular  
306 immunotherapies, immunomodulatory therapies and others, for COVID-19 have been recently  
307 reviewed [67,68].

308

309 **Other adjunct therapies for COVID-19**

310 *Renin-angiotensin system inhibitors*

311 As explained above, ACE2 is expressed in many tissues. ACE2 plays a vital role in the  
312 renin-angiotensin system (RAS), especially in controlling electrolyte balance and blood pressure.  
313 Further ACE2 also extends its role in regulating ARDS and virus-induced lung infections [69]. It  
314 is believed that SARS-CoV-2 infection reduces the expression of ACE2, thereby disrupts the  
315 RAS. A study conducted on the use of ACE inhibitors and angiotensin-II type 1 receptor  
316 antagonists either alone or in combination with other antihypertensive drugs against COVID-19  
317 have shown beneficial effects, such as a reduction in IL-6, and an increase in the CD3 and CD8  
318 population, and also a reduction in the overall viral load. On top of that, the said results have not  
319 been observed in other anti-hypertensive drugs treatments [70]. However, a detailed mechanism  
320 of the efficacy has yet to be investigated. Considering the same mechanism, a few clinical trials  
321 are ongoing (NCT04353596, NCT04330300, NCT04367883, NCT04345406).

322           Apart from the therapeutics/drugs mentioned in the table, other diversified drugs  
323 including antimalarial drugs, antibiotics, antioxidants ( $\alpha$ -Lipoic acid) [71], angiotensin-II type 1  
324 receptor antagonists, vasodilators, and anti-coagulants are being explored in clinical trials  
325 (reviewed elsewhere [72]).

326

### 327 **Nanomedicine**

328           Despite the wide availability of therapeutics, the use of various nanomedicine strategies  
329 has been successful in treating many ailments; precisely, however, its use in pulmonary  
330 drug/therapeutic targeting as an adjunct therapy awaits. Nanoengineering with potential drugs  
331 opens up the possibilities for improved treatment strategies in lung infections. Pulmonary nano-  
332 drug delivery systems offer unique physicochemical properties including mucosal penetrability,  
333 ease of ligand functionalization, enhanced permeation due to small size, increased local  
334 concentrations of drugs and high adjuvant properties for vaccine applications, which make them  
335 ideal drug delivery systems for the treatment of COVID-19-like pulmonary infections (**Fig. 3**).

336

### 337 **Do nanomedicine interventions play a vital role in the management of COVID-19-like** 338 **pulmonary infections?**

339           Regardless of the latest advances in therapeutic modalities for various pulmonary  
340 infections, there is still an unmet medical need to bring advanced nano-targeted therapeutics to  
341 the clinic. ARDS is one of the significant causes of morbidity and mortality across the world,  
342 characterized by acute, diffuse and inflammatory lung injury, which ultimately leads to  
343 refractory hypoxemia [73,74]. Patients with ARDS combat multiple organ failure as they do not  
344 tolerate off-target side effects of various drugs. Besides, ARDS-associated infections are allied  
345 with heterogeneous pathophysiological lung environments [75,76]. The main drawbacks of  
346 conventional pulmonary drug delivery are the lack of alveoli mucosa penetrability, lack of  
347 effectiveness of non-targeted delivery by a systemic route and association of multiple targets at a  
348 single therapeutic site. The past decade's rise in nano-research is now transforming into  
349 considerable commercialization attempts around the globe, and an increasing number of  
350 nanomedical therapies are now approved by the food and drug administration (FDA) and other  
351 agencies [77], from the first approved nano-pharmaceutical (Doxil® liposomal form of  
352 doxorubicin) in 1995 [78]. Nanoengineering with potential drugs opens up possibilities for

353 improved treatment strategies in lung infections. Besides, the unique and/or abnormal signaling  
354 features of the pulmonary endothelium, including vasodilatory molecules (NO, prostacyclins)  
355 and enhanced expression of leukocyte-binding molecules (like ICAM and VCAM) [79] may play  
356 a potential role in nanocarrier binding for reducing ARDS-associated pulmonary embolisms (PE)  
357 and pulmonary arterial hypertension (PAH) diseases.

358 Nanoparticles have shown significant potential advantages for the delivery of antiviral  
359 molecules [80,81]. In addition, nanoparticles display direct antiviral activity. Up to date, various  
360 forms of nanoparticle systems have been reported to exhibit antiviral activity including silver  
361 nanoparticles, functional gold nanoparticles, and quantum dots [82]. For instance, the widely  
362 used strategy by most of the 'antiviral' nanoparticles include blocking the viral attachment or  
363 viral entry into the host cells. Unfortunately, at the latter stage, the 'antiviral' nanoparticles have  
364 no suppressive effect on the progeny of the virus in their late phase of replication. In addition,  
365 despite challenges [83,84], numerous studies have reported on nanoparticle based drug therapies  
366 against respiratory tract infections, e.g. selenium-, silver-, PEG-PLGA-nanoparticles against the  
367 influenza (H1N1) virus. These nanoparticle based systems have shown an increased therapeutic  
368 efficacy and reduced associated toxicity compared to free drugs (reviewed in [85]). Interestingly,  
369 among these features, their mucoadhesive property presents a significant priority in designing  
370 nanoparticle-based therapies against respiratory infections; this could delineate the capacity of  
371 targeted delivery to the lungs. To achieve this high mucoadhesive property, several modifications  
372 of nanomaterials via various functionalization mechanisms have been developed (**Fig. 3**) [81].

373 Development of the disease-responsive nano delivery system originated by considering  
374 their unique interactions, such as hydrogen bonding, hydrophobicity, ionic bonding, and others.  
375 Also, selective functionalization, including thiols, catechols, acrylates, and others, have proven  
376 their increased covalent interaction with mucin glycoproteins. Furthermore, polymers, such as  
377 cellulose, chitosan, pectin, alginate, and others have also bound in a noncovalent manner [84].  
378 Among these polymers, chitosan nanoparticles have shown encouraging results for targeted drug  
379 delivery. Bioavanta-Bosti, a pioneer company in chitosan nanoparticle science, has begun a  
380 proof-of-concept study on a chitosan-based aerosol system namely "Novochizol aerosol". This  
381 system is used for the delivery of drugs like losartan, valsartan, telmisartan, and digoxin, which  
382 may have a potential role in the battle against the coronaviruses [86] Chitosan can be seen as a  
383 major player since it has unique mucoadhesive properties due to the interaction between

384 positively charged chitosan and negatively charged mucus [87]. This is an effective way to  
385 improve the retention time of the drugs in the lungs, and hence might have enhanced clinical  
386 efficacy through prolonged lung retention.

387

### 388 **Rationale applications of nanomedicine against Coronaviruses**

389 One of the possible strategies to fight against SARS-CoV-2 could implicate the  
390 prevention of viral entry into the host cell. It is well known that blockage of viral surface proteins  
391 can lead to virus inactivation, so that targeted nanoparticles specific to virus-expressed proteins,  
392 could minimize viral internalization. In our latter portion, we have unfolded the role of metallic  
393 and metallic-based nanoparticles in blocking viral proteins and, thus, preventing possible viral  
394 entry. Another way to deliver antivirals (such as zidovudine, acyclovir, dapivirine, and efavirenz)  
395 is to enhance drug bioavailability by using organic nanoparticles (such as albumin and gelatin)  
396 and virus-specific targeting proteins (reviewed elsewhere [85]). This approach would provide a  
397 dual benefit as it can lead to the successful delivery of drugs along with the targeted antiviral  
398 activity.

399

### 400 **Nanomedicine in immunotherapy, vaccines and vaccine adjuvants**

401 Many flu (influenza) vaccines, such as Inflexal® V, Influvac® Plus, and others, were  
402 approved for clinical use against influenza infections [85,88]. However, the use of vaccines is the  
403 most excellent strategy to combat COVID-19 like diseases, their discovery time-line, stability,  
404 and delayed mechanism of action (production of immunological memory against target antigens)  
405 making them a second choice of therapies. Nevertheless, therapeutic and prophylactic strategies  
406 are under development to address current and potential future coronavirus infections, including  
407 effective vaccines. As previously discussed, the essential genomic match between SARS-CoV-2  
408 and other coronaviruses help the pharma industry and academic institutions design appropriate  
409 vaccine candidates.

410 The development of COVID-19 vaccine candidates relies on several high-tech platforms  
411 including attenuated and inactivated viruses, replicating and non-replicating viral vectors, DNA  
412 and mRNA, virus-like particles, and recombinant protein-based approaches. Some platforms  
413 offer vital advantages, such as viral vectors, which offer strong immune responses, superior  
414 protein expression, and prolonged stability. On the other hand, DNA or mRNA offer antigen

415 manipulation flexibility [89]. In contrast, the recombinant protein-based development approach  
416 is more comfortable for scaling up vaccine doses using existing production capabilities. To date,  
417 213 vaccines are in development, and 35 are in clinical testing [90]. The main strategy for most  
418 of the vaccine candidates is to induce antibodies against the viral S protein, averting the ACE2-  
419 mediated host uptake. In the case of SARS-CoV vaccine development, higher antigen-specific  
420 antibody titers and better protection were reported with the S protein subunit vaccines when  
421 compared to any other target strategy. SARS/MERS vaccine development research has suggested  
422 that S protein subunits and RBD of the S1 subunit as the most preferred target sites [91]. As  
423 complete knowledge on the SARS-CoV-2 specific antigens are limited, traditional vaccinology  
424 methods in combination with nanotechnology would be beneficial.

425         Recent data from a team of researchers at UC San Diego highlighted the role of  
426 nanotechnology in COVID-19 vaccine development [90]. From a vaccine engineers' point of  
427 view, nanomedicine offers them an ideal platform for the delivery of antigens, serving as  
428 adjuvant platforms, and mimicking viral structures. As cellular immune responses are essential to  
429 combat viral infections, vaccines and vaccine adjuvants, which elicit Th1-biased immune  
430 responses, are preferred in COVID-19 like diseases. It is important to note here that in most of  
431 the cases humoral immune responses have been observed for most adjuvants and delivery  
432 platforms while only viral vectors, immune stimulating complexes (ISCOMs) and Montanide™  
433 have shown cytotoxic T cell responses in the clinic [92]. Recent reports indicate that  
434 nanoparticles allow multivalent antigen presentation and stabilization of antigens upon  
435 administration. They can also serve as adjuvants for boosting immune responses and as carriers  
436 for targeted antigen delivery [93]. Indeed, an mRNA vaccine delivered by a liposomal  
437 nanoparticle is amongst the candidates currently in clinical trials against SARS-CoV-2 [94].

438         Among the different types of vaccines, subunit and DNA/RNA vaccines have gained  
439 much attention, due to their fewer side-effects, low cost, and ease of preparation [95]. Often  
440 subunit vaccines require vaccine adjuvants and substances/compositions that increase the  
441 immunogenicity of the targeted antigens. More information could be found in our recent review  
442 [92]. Further, stability and tissue-specific targeting issues are limiting their success [93].  
443 Therefore, the use of nanomedicine has become an attractive and quick strategy to address these  
444 limitations, mainly needed for COVID-19 like pandemics. For example, we have used an oleic  
445 acid nanoemulsion system to increase the antigen uptake capacity of mucosa (in the nasal



446 epithelial). These featured nanomaterials would be advantageous to use as targeted delivery  
447 vehicles for the respiratory tract [96].

448 Few exciting studies have been documented on nanotechnology-based vaccine  
449 developments against SARS-CoV-2. Erasmus et al. developed an *Alphavirus*-derived replicon  
450 RNA vaccine candidate (repRNA-CoV2S), which is composed of the SARS-CoV-2 spike  
451 protein replicons in the squalene-based emulsion of lipid inorganic nanoparticles (LION) [97].  
452 Superparamagnetic iron oxide ( $\text{Fe}_3\text{O}_4$ ) and cationic lipid 1,2-dioleoyl-3-trimethylammonium  
453 propane were used as inorganic and lipid source in the nanoparticles, respectively. Immunization  
454 of this vaccine in mice and macaques produced antigen-specific antibody responses, which were  
455 comparable to the convalescent response from COVID-19 [97]. The superiority of the vaccine  
456 composition is that it elicited robust long-term antibody responses against SARS-CoV-2 upon  
457 single-site intramuscular injection. Having squalene, a gold standard oil-based vaccine adjuvant,  
458 in the nanoparticle composition, it is anticipated to induce Th1-mediated cellular and robust  
459 antibody responses [92]. Besides, taking into consideration that older people are more prone to  
460 SARS-CoV-2 infections, the authors have studied the vaccine candidate responses in young and  
461 old mice. Vaccine candidates produced SARS-CoV-2 neutralizing antibodies effectively with  
462 and without multiple injection schedules. Furthermore, their two-vial approach, which contains a  
463 LION in one vial and repRNA in another vial, are easier to scale up than the complexed  
464 formulations [97].

465 In addition, carbon-nanomaterials have also been explored recently as novel anti-viral  
466 agents owing to their unique physicochemical properties. Garg et al. proposed conceptual  
467 insights into a series of bioisosteres derived from triazole functionalized heteroatom co-doped  
468 carbon quantum dots (TFH-CQDs) and design of peptide inhibitors to combat human  
469 coronavirus either by blocking the viral entry or inhibiting the viral enzymes for replication, such  
470 as helicase and 3CLpro [98].

471 NVX-CoV2373 is another COVID-19 nanoparticle vaccine candidate [99], which is  
472 composed of trimeric full-length recombinant spike glycoproteins of SARS-CoV-2 and Matrix-  
473 M1 adjuvant (the combination of different purified fractions of saponins from the tree *Quillaja*  
474 *Saponaria* Molina with cholesterol and phospholipid) [100]. Preclinical studies have shown its  
475 potency by eliciting anti-spike IgG antibodies with hACE2 receptor blocking, and virus  
476 neutralization capacity. Besides, it induced both T and B cell responses [99]. By considering the

477 above merits, the vaccine candidate has been taken for clinical evaluation (Phase 1-2;  
478 NCT04368988). The safety and immunogenicity studies of this vaccine was conducted on 131  
479 healthy adults [101]. Results revealed that the vaccine is safe and induced optimal immune  
480 responses. Preferably, the said adjuvant should enhance a Th1 polarized response. The vaccine  
481 benefited from the adjuvant in terms of dose sparing and enhanced immune response [101].

482 Huan et al. studied the CoVaccine HT™ adjuvant effect against the SARS-CoV-2 spike  
483 S1 protein in mice [102]. The CoVaccine HT™ is an oil-in-water emulsion type, which is  
484 composed of negatively-charged sucrose fatty acid sulphate ester and squalene (source: plant-  
485 derived) [103]. Importantly, this vaccine adjuvant has proven its potency and efficacy in  
486 different vaccine formulations, including malaria, ebola, Zika, and others [104-106]. For  
487 comparison of adjuvant activity against SARS-CoV-2, alum (a gold standard in the family of  
488 adjuvants), and Th2 adjuvant, were used in the study. The CoVaccine HT™ induced high  
489 antigen-specific antibody titers, class switching response, cell-mediated immune responses and  
490 virus-neutralizing antibody titers, which are more significant than the alum. One of the recent  
491 studies by Rao L et al., utilized the nano biotechnological approach to formulate nanodecoys  
492 with cellular membrane nanovesicles derived from genetically edited 293T/ACE2 and THP-1  
493 cells. The nanodecoys with biological properties have abundant ACE2 and cytokine receptors,  
494 which compete with host cells and significantly inhibited viral replication and infection [107]. Of  
495 note, a detailed discussion of nanotechnology-based vaccine development against COVID-19 has  
496 been covered in recent reviews [108-112].

497

### 498 **Nanomedicine as therapeutic agents**

499 As explained earlier, being the prime receptor of SARS-CoV-2, ACE2 has become a  
500 vibrant target for most therapeutic and prophylactic strategies. Recently, Wang et al., have  
501 developed a biocompatible, cell membrane derived nano-antagonist particulate system prepared  
502 from ACE2-rich cells by a simple, cost-effective membrane extrusion method. These synthesized  
503 particles termed as HEK-293T-hACE2 NPs contained 265.1 ng/mg of ACE2 on the surface of  
504 the particles and acted as a plug to trap SARS-CoV-2 S1 in a competitive dose-dependent  
505 manner. Being highly interactive to ACE2, it inhibited the SARS-CoV-2 pseudovirus entry into  
506 renal tubular cells [113]. Thus, it is clear that nanotechnology could support the conception of  
507 therapeutic tools for inhibiting viral and host interactions.

508 In an effort to improve the next generation of nano-engineered delivery mechanisms,  
509 research has been focused on incorporating therapeutic benefits in order to provide safe and  
510 efficient nano-platforms to combat COVID-19-like and other types of pulmonary infections. The  
511 success of nanomedicine as an antiviral therapy has been already proven in COVID-19-like  
512 pulmonary infections. One such example is Middle East Respiratory Syndrome Coronavirus  
513 (MERS-CoV), which has been identified as an infective virus with high pathogenicity and  
514 mortality rate [114]. MERS-CoV can cause severe respiratory illnesses and is recognized as a  
515 severe threat to public health. Currently, there has been no vaccine or effective treatment for  
516 MERS, and its treatment mainly relies on supportive measured and combination therapy of  
517 traditional antiviral drugs, such as interferon and ritonavir [115]. However, neither of them  
518 showed good antiviral effects in patients, leading to limited therapeutic applications. One of the  
519 possible reasons for an increasing number of MERS-CoV infections was due to spike protein (S  
520 protein)-mediated membrane fusion between MERS-CoV and host cells [116-118]. Recently,  
521 Ning and his team developed a novel gold nanorod-based peptide inhibitor to fight against  
522 MERS. The peptide showed good inhibitory activity against the S protein-mediated membrane  
523 fusion, and more importantly the designed gold nanorods enhanced inhibitory viral activity. The  
524 peptide-functionalized gold nanorods improved biostability and biocompatibility and had better  
525 physical and pharmaceutical profiles than those of the peptide alone, endowing potential clinical  
526 applications for the treatment of MERS (see **Table 2** for more information, **Fig. 4**) [119].  
527 **Though nanotechnology offers a wide range of diagnostics techniques, SARS-CoV-2 specific**  
528 **diagnostic methods (e.g., biosensors) have yet to be fully developed [120,121].**

529 To deliver antibiotics locally with increased therapeutic efficacy, various nano-  
530 engineered approaches, such as liposomal formulations, have been reported for lung delivery  
531 [122-124], which are intended to increase permeation and intracellular drug delivery. Such  
532 strategies provide insights into future clinical targeting systems with improved therapeutic  
533 responses to fight pulmonary infections.

534 Interestingly, the MERS-CoV spike (S) protein is responsible for receptor binding and  
535 entry into cells. It is an immunodominant antigen and induces neutralizing antibodies in the host.  
536 Both of these characters make the S protein a perfect candidate for anti-MERS-CoV vaccines.  
537 Coleman et al. reported that MERS-CoV S nanoparticle-based vaccination in mice induced a  
538 higher neutralizing antibody response to the S protein and protected the mice against a viral

539 challenge [125]. Such functionalized nanoparticle formulation systems could help to pave the  
540 way to develop new platform strategies to combat COVID-19-like respiratory diseases.

541 In addition to the liposomal strategies, polymeric nanosystems [126,127] also enhance  
542 the localization of the drug in the lung regions and boost the therapeutic response. In an attempt  
543 to improve immunization approaches to strengthen immune responses, hollow viruses, such as  
544 particulate matter constructs (virus-like particles-VLPs), deficient in genetic material could  
545 induce a robust immune response or improve the response to lung-related infections and are  
546 worth exploring in the immediate future for specific pulmonary infections [128,129].

547 Semiconductor nanocrystals such as quantum dots (QD) have also offered a wide range  
548 of peculiar properties attractive for treating viruses, including size-dependent optical and  
549 electronic properties [130]. Due to their distinguished luminescent properties, such as broad  
550 excitation spectroscopy, narrow and bright emission spectroscopy, long fluorescence lifetime,  
551 and size-dependent emission wavelengths, QDs have indeed shown hopes for virus-cell  
552 labelling, detection and image tracking. By using a pig coronavirus porcine epidemic diarrhoea  
553 virus (PEDV) as a model, recently Du et al. have demonstrated that Ag<sub>2</sub>S nanocrystals (NC)  
554 have an excellent viral inhibitory ability with a different mechanism of action from other  
555 functional nanoparticles [82]. In addition to the inhibition of viral negative-strands generation  
556 and viral budding, Ag<sub>2</sub>S NC has also induced IFN-stimulated genes and the expression of several  
557 pro-inflammatory cytokines [82]. Moreover, the Ag<sub>2</sub>S NC were also shown to have comparable  
558 virus inhibitory effects on other RNA viruses, such as porcine reproductive and respiratory  
559 syndrome virus (PRRSV). Therefore, Ag<sub>2</sub>S NC has been identified to have broad-spectrum  
560 antiviral properties against RNA viruses [82]. Recent studies have shown that silver  
561 nanoparticles display antiviral activity against influenza A virus, hepatitis B virus, human  
562 parainfluenza virus, herpes simplex virus, and human immunodeficiency virus [131], which  
563 provide other types of therapeutic opportunities for combating pulmonary-associated infections.  
564 Recent reports describe the antiviral activity of silver or gold nanoparticles against DNA or RNA  
565 viruses. The possible mechanism of silver and other metal plasmonic nanoparticles is shown in  
566 fig. 4. Apart from functionalization and targeting groups present on the nanoparticle surface, the  
567 mode of action is also dependent on the shape and size, which could interact with virus particles  
568 with a well-defined spatial arrangement. In recent years, scholars have paid more attention to the  
569 use of traditional medicine for fighting viruses [21]. The antiviral effects of traditional medicine

570 might be associated with inhibiting the replication of viruses. Besides, they might improve  
571 respiratory virus-mediated lung damage [132].

572 Over the years, textile industries have been using different inorganic/metal nano-  
573 composites (alginate, copper, gold, zinc, magnesium, silver, titanium, and others), which would  
574 protect textiles from diversified microbes [133]. Although inorganic reagents have been used as  
575 broad-spectrum antimicrobial compounds, the drawback of their instability limits their use, e.g.,  
576 silver vigorously reacts with  $\text{Cl}^-$ ,  $\text{HS}^-$ , and  $\text{SO}_4^{2-}$ , and others lose antimicrobial capacity [133]. To  
577 overcome this, a nanotechnology-based strategy, which increases the stability of the silver has  
578 gained much attention. Recently, silver nanoparticles prepared with the acrylic-based polymers  
579 in polycotton fabrics have shown a significant antimicrobial effect, including SARS-CoV-2  
580 (SARS-CoV-2/human/BRA/SP02cc/2020-MT350282) [134]. The possible mechanism behind  
581 the antimicrobial, and in particular antiviral effect is explained by two pathways. First, silver  
582 nanoparticles prevent the viral attachment to the host cells by interacting with virus surface  
583 glycoproteins via a sulfur linkage. Second, these nanoparticles interact with transcription factors,  
584 which are required for virus replication. However, the exact mechanism is yet to be established  
585 [134].

586 Du et al. have developed a unique one-step method in which they have used curcumin to  
587 prepare uniform and stable cationic carbon dots (CCM-CDs) with antiviral properties [135,136].  
588 Curcumin has already proven its effectiveness against various infections and exhibits antiviral  
589 activity by reducing viral RNA expression, protein synthesis, and virus titers. In addition, it was  
590 found to have a protective effect on cells against virus-induced apoptosis and cytopathic activity  
591 [137]. The authors studied the inhibitory performance of CCM-CDs on viral replication. In their  
592 study, they have selected PEDV as a coronavirus model. Most importantly, their findings suggest  
593 that the developed CCM-CDs inhibit the proliferation of PEDV with much higher efficiency than  
594 non-curcumin modified carbon dots (**Fig. 5**) [136].

595 Besides, nanotechnology applications have advanced to develop personalized patient  
596 management, including preparation of naso-delivery vehicles (for the easy administration of  
597 drugs by an intranasal route), insufflations (to deliver the drug directly to lungs), and others. The  
598 use of inorganic-polycotton fabrics (explained earlier) has been one of the best strategies for  
599 contagious diseases [134]. In order to combat the spread of coronavirus, the use of adequate  
600 personal protective equipment (PPE), including masks, gloves, medical aprons and kits, are also

601 necessary [138]. Antimicrobial activity is imparted by the use of inorganic based nanoparticle  
602 coatings, which could be used in various types of fibers or materials, and also fabricating such  
603 cloths with anti-viral agents could be an interesting approach to minimize the spread of the virus.  
604 Moreover, there is a wide scope to consider the novel nano-strategies to combat emerging  
605 microbes, e.g., development of face/mouth masks, which are composed of stable and safety  
606 antimicrobial inorganic composites (with antibiotics/antiviral coatings, e.g., silicon nitride)  
607 [139,140]. Although these nano-inorganic composites exhibit less allergic responses, detailed  
608 toxicity parameters should be sensibly evaluated. As composites are in the nano-range, there is a  
609 chance of ingestion and toxicity due to the accumulated composites.

610 Future nanocarrier research with specific ligand functionalization to target the afore-  
611 mentioned molecules are likely to enhance their therapeutic efficacy by avoiding off-targeted  
612 drug side effects. The advantages of their large surface-to-volume ratios, the high surface area  
613 activity and the size-dependent optical and electronic properties of nanocarriers, which are  
614 widely explored in the field of biosensors and biomedicine, and their viricidal activity, have also  
615 been systematically investigated. All of these properties make nanoparticles a strong potential  
616 weapon to fight against COVID-19-like pulmonary infectious diseases in the near future.

617

## 618 **Conclusion and future outlook**

619 The complete genome sequencing of SARS-CoV-2 revealed a close homology with other  
620 CoVs, including SARS-CoV and MERS-CoV. In particular, viral enzymes such as 3CL protease,  
621 helicase, papain-like protease, and RNA-dependent RNA polymerase and their active sites are  
622 highly conserved across other CoVs. However, a better understanding of the SARS-CoV-2  
623 tropism would benefit for therapeutic purposes. In addition, the controversial effects of immune  
624 cells on secondary injuries warrant further investigation. Finally, many other endogenous  
625 protective factors that help in preventing tissue injury and innate repair functions are all  
626 unanswered questions that need to be explored further. The use of immunomodulatory therapies  
627 may not clear the virus load but have the potential to reduce the severity of the disease caused by  
628 the cytokine storm, details that we emphasized on the 'cytokine storm' should also support future  
629 vaccine research on COVID-19.

630 Until today, a few questions remain unclear including the best suitable therapeutic  
631 strategy to fight against COVID-19 and associated lung infections. The past decade, however,

632 has witnessed the use of several combination strategies during numerous pandemics and other  
633 viral infections like HIV and influenza. Therefore, the use of a broad-spectrum antiviral agents in  
634 combination is advisable against COVID-19 and nanomedicine is primed to be central for any  
635 solutions due to its attractive properties as mentioned above. Currently, the scientific community  
636 is globally juggling many drugs to find suitable and/or manageable therapeutic options against  
637 COVID-19. Despite initial encouraging preliminary results in short cohorts, a tremendous effort  
638 is needed for targeted approaches, however, the time spent now will help with all future  
639 pandemics as nanomedicines can be a platform for numerous viruses, requiring simply to be  
640 functionalized with different regions that target different viruses. Worthwhile bioinformatic  
641 studies have come up with several druggable proteins and repurposing drugs, and rationalization  
642 of these drugs for the future use would be prudent [58,59].

643

644

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656 Conception, S.R.B, T.J.W. Literature Survey and Writing, S.R.B., N.G.K, and R.A.B.

657 Editing and Reviewing, T.J.W, Y.R, and J.B.

658 Final Approval, All the authors.

659

660 **Declaration of interests**

661 None

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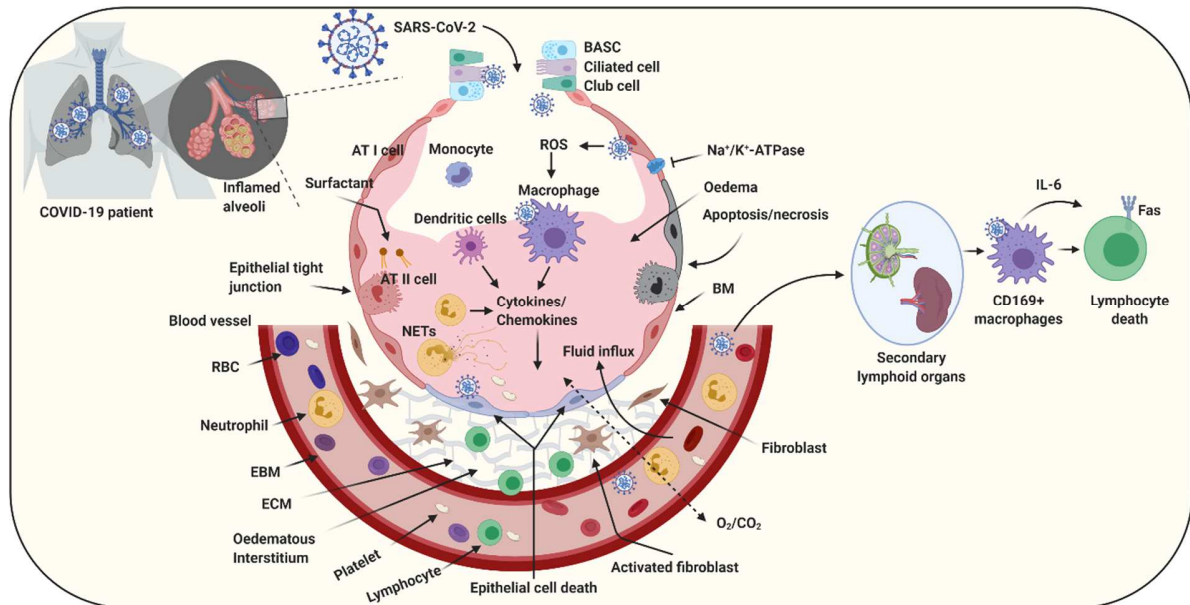
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1076 **Figures**

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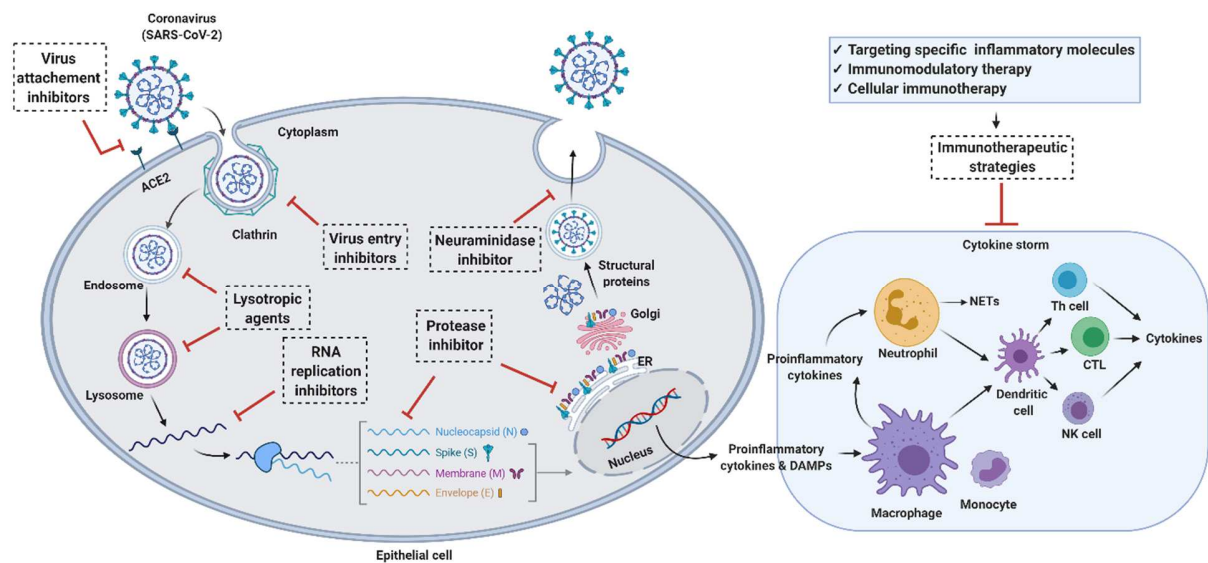
1080 **Fig. 1. Lung pathology in COVID-19.** The lungs of severely ill COVID-19 patients appear to  
 1081 be opaque in the CT scan. SARS-CoV-2 enters via the nose, mouth, or eyes and reaches the  
 1082 alveoli, where a high expression of ACE2 receptors are present. Alveoli exist in the form of  
 1083 balloon-shaped structures. In any lung infection, different cells and substances are involved in  
 1084 protective immunity as well as inflammation. Invading SARS-CoV-2 interacts with, especially,  
 1085 tracheobronchial and alveolar epithelium and subsequently induces damage (apoptosis/necrosis)  
 1086 to the cells. The damage affects the tight barrier integrity of both the endothelium and epithelium  
 1087 layers. The epithelium is composed of a monolayer of alveolar type I and alveolar type II cells,  
 1088 which perform gas exchange and the production of surfactant functions, respectively. These  
 1089 functions keep the air space dry in the lungs. The damaged cells produce danger signals, such as  
 1090 reactive oxygen/nitrogen species, which recruit the innate immune cells, such as monocytes,  
 1091 immature macrophages, neutrophils, and dendritic cells. Upon uncontrolled activation, immune  
 1092 cells, epithelial cells, and fibroblast cells secrete copious amounts of pro-inflammatory cytokines  
 1093 and chemokines, which in turn act as a causative factor for epithelial cell death. In addition, they  
 1094 block the functional  $\text{Na}^+/\text{K}^+$ -ATPase pump, which keeps the osmotic equilibrium in the alveolus.  
 1095 The impaired tight junctions lose their fluid resistance nature and allow the fluids into the  
 1096 alveolus leading to edematous inflammation, which obstructs the vital gas exchanges process.

1097 Note: This hypothetical figure illustration is based on the output obtained from different non-  
 1098 peer reviewed publications and in comparison of other lung diseases, such as ARDS, SARS,  
 1099 MERS, influenza.

1100 Abbreviations: ATI, alveolar type I cell; ATII, alveolar type II cell; BASC, bronchioalveolar  
 1101 stem cell; BM, basement membrane; EBM, endothelial basement membrane; ECM, extracellular  
 1102 matrix, NETs, neutrophil extracellular traps; RBC, red blood cell; ROS, reactive oxygen species.

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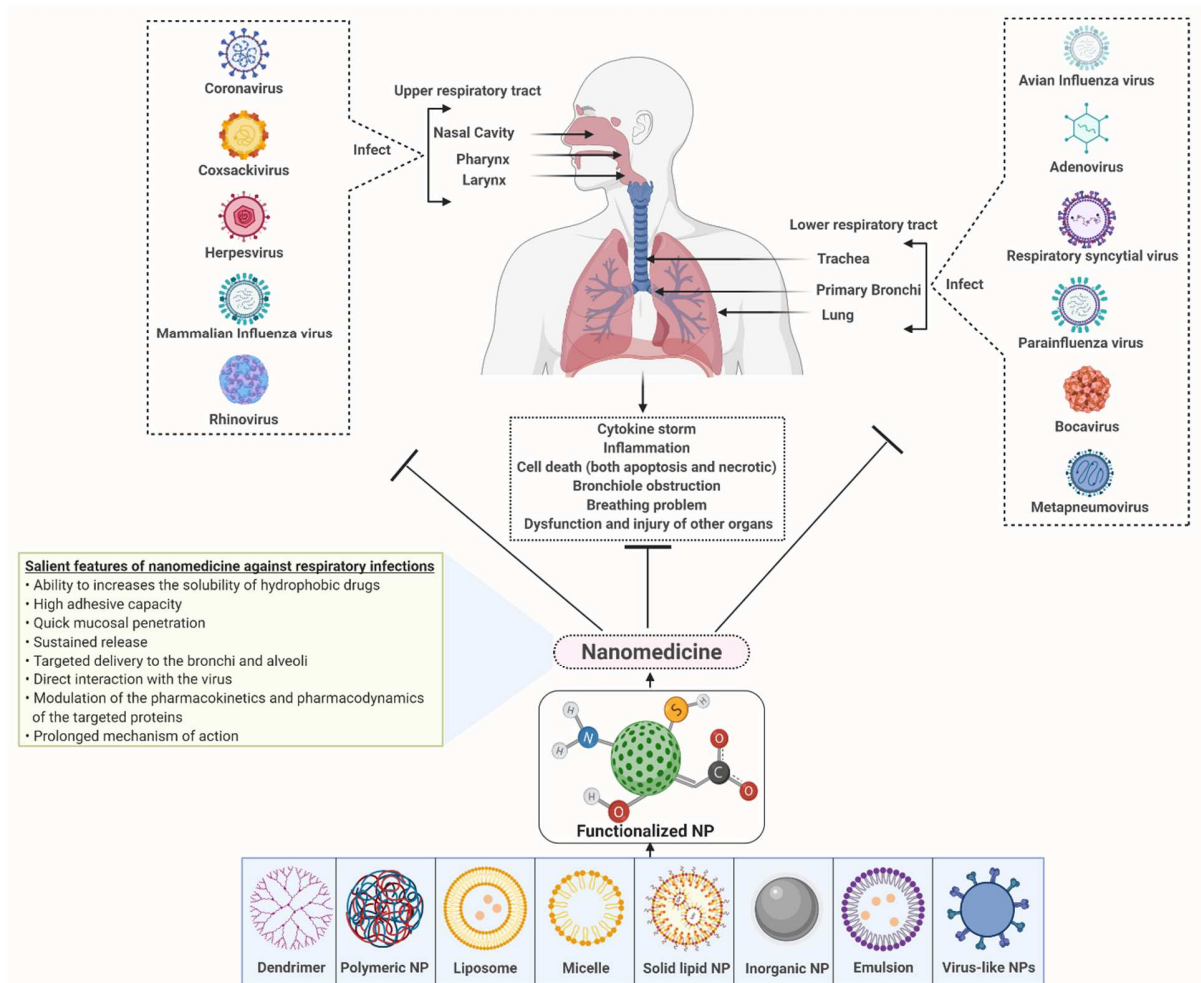
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**Fig. 2. Therapeutic strategies for COVID-19.** SARS-CoV-2 uses epithelial cells, particularly lung epithelial cells, for their propagation. During the replication process, virus particles induce cell death signals to release pro-inflammatory cytokines and DAMPs, which in turn are sensed by the macrophages, monocytes, and neutrophils followed by the activation of other bystander cells and the development of the systemic cytokine storm. Based on the life-cycle of SARS-CoVs, the above-proposed drugs have been used in clinical trials. Note: As detailed, immunological responses of SARS-CoV-2 have not been established yet; thus, studies illustrated are in comparison with SARS and MERS. More details can be found in the text and table 1. Abbreviations: ACE2, angiotensin 1-converting enzyme 2; CTL, cytotoxic T lymphocytes; DAMPs, danger-associated molecular patterns; ER, endoplasmic reticulum; NETs, neutrophil extracellular traps; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1140 **Fig. 3. Nanomedicine based strategies to prevent the pathologies associated with**  
1141 **respiratory infections.** A variety of viruses from different sources are responsible for  
1142 respiratory infections. Few viruses, such as rhinovirus, parainfluenza virus, coronaviruses,  
1143 adenoviruses, coxsackievirus, respiratory syncytial virus, herpesvirus, bocavirus, and others,  
1144 particularly infect the upper respiratory tract. On the other hand, influenza virus, parainfluenza  
1145 virus, respiratory syncytial virus, bocavirus, adenoviruses, metapneumovirus, and others infect  
1146 the lower respiratory tract. In both the cases, they cause the common cold, bronchitis,  
1147 bronchiolitis, and sometimes-severe pneumonia. Furthermore, the infection results in the  
1148 dysfunction and damage to the other vital organs. Nanomedicine-based strategies that are  
1149 explained above target the pathologies and reduce the severity of the disease.

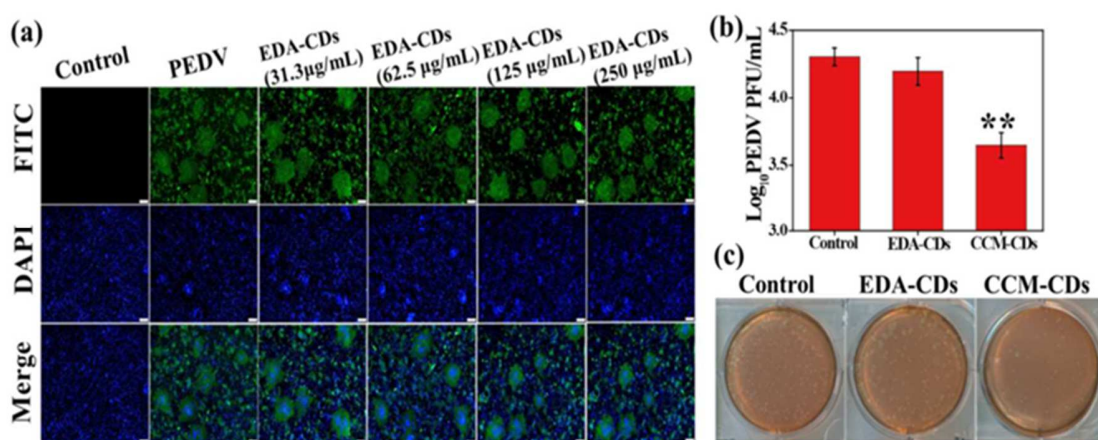
1150 Abbreviations: NP, nanoparticle



1170 play a potential role in the diagnostic and therapeutic of COVID-19 like diseases. NPs are useful  
1171 for the development of different sensors to detect SARS-CoV-2-like infections and, thus, can be  
1172 used for an early real-time detection of virus with precession. A therapeutics approach at the  
1173 moment is based upon the post functionalization strategies by using different biomolecules and  
1174 small molecule inhibitors to prevent the entry of the viruses inside the host cells and to block  
1175 viral replication.

1176 Abbreviations: AuNPs, gold nanoparticles; COVID-19, coronavirus disease 2019; DDP4,  
1177 dipeptidyl peptidase four receptors; 6-HB, 6-helix bundle; HR, heptad repeat; QDs, quantum  
1178 dots; MERS-CoV, Middle East respiratory syndrome-related coronavirus; NPs, nanoparticles;  
1179 VLPs, virus-like particles

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1185 **Fig. 5. The effect of EDA-CDs on PEDV.** (a) The effect of different concentrations of EDA-  
1186 CDs on PEDV-infected Vero cells by indirect immunofluorescence assay. Scale bar: 100 µm. (b)  
1187 The titers of PEDV when exposed or unexposed to 125 µg/mL EDA-CDs or CCM-CDs. All  
1188 error bars were determined according to the three replicate experiments. \*\* p < 0.01 and  
1189 indicates superior antiviral activity of CCM-CDs to EDA-CDs treated and untreated, against  
1190 PEDV. (c) Virus titers were calculated in the presence and absence of EDA-CDs or CCM-CDs.  
1191 Pictures were taken at 12 hpi. Figure is reproduced from ref [136]. Copyright 2018 American  
1192 Chemical Society.

1193 Abbreviations: CCM-CDs, curcumin carbon dots; EDA-CDs, ethylenediamine carbon dots;  
1194 PEDV, porcine epidemic diarrhoea virus

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1200 **Tables**

1201 **Table 1. Therapeutic strategies for COVID-19\*. Below is a list of drugs currently being**  
 1202 **explored for repurposing against COVID-19.**

Type of therapeutic strategy	Drug candidate	Comment
<i>Antiviral therapy</i>		
Protease inhibitors	Camostat mesilate, lopinavir/ritonavir, darunavir/cobicistat, ASC09, Danoprevir, Boceprevir, GC376	<ul style="list-style-type: none"> <li>• In a clinical study on a small cohort of Taiwan COVID-19 patients, lopinavir (200 mg)/ritonavir (50 mg) did not shorten the duration of viral shedding [142].</li> </ul>
Nucleoside reverse transcriptase inhibitors	Azvodine, Emtricitabine/Tenofovir	<ul style="list-style-type: none"> <li>• It exhibited high potency anti-HIV-1 activity [143].</li> </ul>
Neuraminidase inhibitors	Oseltamivir	<ul style="list-style-type: none"> <li>• It is licensed for influenza A and B treatment.</li> <li>• It has been used either alone or in combination for the treatment of COVID-19 (n=124). Although many patients have recovered, the doses used in combination had no effective outcome [144].</li> </ul>
RNA polymerase inhibitors	Remdesivir, Ribavirin, Favipiravir	<ul style="list-style-type: none"> <li>• These drugs mainly come under the category of nucleoside analogues.</li> <li>• Although remdesivir was developed for the treatment of Ebola [145] and Marburg [145,146], it has exhibited antiviral therapy against SARS and MERS [147]. In addition, molecular docking studies also supported their anti-SARS-CoV-2 function [148].</li> <li>• Interestingly, ribavirin has been listed in the WHO essential medicine list (21<sup>st</sup> list in 2019). Though meta-analysis data has not shown significant clinical benefit for ribavirin against SARS [149] and MERS [150], the use as a drug candidate against COVID-19 should not be neglected.</li> <li>• Favipiravir is approved to treat influenza infection and currently evaluated in phase III</li> </ul>

		clinical trials against COVID-19 [151].
Viral fusion inhibitor	Umifenovir (Arbidol)	<ul style="list-style-type: none"> <li>• Arbidol is mainly prescribed for the treatment of upper respiratory tract infections, mainly caused by the influenza virus [152].</li> <li>• A retrospective study on arbidol in COVID-19 patients (n=257) showed high efficacy with reduced mortality rate than other antiviral agents [153].</li> </ul>
Viral endonuclease inhibitor	Baloxavir marboxil (Xofluza)	<ul style="list-style-type: none"> <li>• It acts against the influenza virus and is approved by the FDA [154].</li> </ul>
Virus attachment inhibitors	Camostat mesylate, Nafamostat mesylate (Fusan)	<ul style="list-style-type: none"> <li>• It is used to treat pancreatitis.</li> <li>• Nafamostat mesylate is used to treat acute pancreatitis.</li> <li>• Nafamostat mesylate inhibits SARS-CoV-2 spike protein-interaction with the host cell surface receptors [12].</li> </ul>
<i>Immunotherapies and inhibitors of inflammation</i>		
IL-1 receptor antagonist	Anakinra	<ul style="list-style-type: none"> <li>• It blocks the IL-1-mediated pro-inflammatory effects.</li> <li>• It has shown a beneficial effect in rheumatoid arthritis patients [155].</li> <li>• Under evaluation at various centers for severe COVID-19 cases [156,157]</li> </ul>
Janus kinase inhibitor	Baricitinib	<ul style="list-style-type: none"> <li>• Baricitinib selectively inhibits Janus kinase (JAK1/JAK2) and gp130 family cytokines, primarily type I IFN-mediated immune responses.</li> <li>• Baricitinib also blocks the viral entry by inhibiting AP2-associated protein kinase one and cyclin G-associated kinases.</li> <li>• Under evaluation at various centers for severe COVID-19 cases [158,159]</li> </ul>
TNF inhibitor	Adalimumab (Humira)	<ul style="list-style-type: none"> <li>• Adalimumab is a recombinant monoclonal antibody against TNF responses, which is approved for the treatment of autoimmune disease, particularly rheumatoid arthritis (RA)</li> </ul>



		[160].
Janus kinase inhibitor	Ruxolitinib	<ul style="list-style-type: none"> <li>• It is approved for the treatment of myelofibrosis [161].</li> </ul>
Anti-VEGF	Bevacizumab	<ul style="list-style-type: none"> <li>• A humanized anti-VEGF monoclonal IgG1 antibody.</li> <li>• It was approved and available for the treatment of different cancers (advanced colorectal cancer, advanced non-small cell lung cancer, metastatic breast cancer, advanced glioblastoma multiforme, and advanced renal cell cancer) either alone or in combination [162].</li> </ul>
Complement inhibitor	Eculizumab (Soliris, Elizaria)	<ul style="list-style-type: none"> <li>• A humanized monoclonal antibody against complement C5.</li> <li>• It is approved and available for the treatment of complement induced paroxysmal nocturnal hemoglobinuria [163].</li> <li>• Under evaluation for severe COVID-19 cases [164,165].</li> </ul>
DAMPs regulators	CD24Fc	<ul style="list-style-type: none"> <li>• CD24Fc is a fusion protein to selectively inhibit DAMP-associated inflammation.</li> <li>• It is currently under clinical (phase III) evaluation against GvHD [166].</li> </ul>
Sphingosine-1-phosphate receptor modulator	Fingolimod (FTY720)	<ul style="list-style-type: none"> <li>• Acts as a sphingosine-1-phosphate receptor regulator.</li> <li>• It inhibits the egress of lymphocytes into the systemic circulation and approved for the treatment of MS [167].</li> </ul>
Viral replication inhibitors	Interferon $\beta 1\alpha$ , Recombinant human interferon $\alpha 1\beta$ , $\alpha 2\beta$	<ul style="list-style-type: none"> <li>• Activation of type I IFN signals through JAK–STAT pathway enhances the virus killing capacity of cells.</li> <li>• An open-labelled study conducted on medical staff (n=2944) with recombinant human IFN-<math>\alpha</math> nasal drops with or without thymosin-<math>\alpha 1</math> shown potential preventive effect from COVID-19 infection [168].</li> </ul>

Viral entry inhibitors	Meplazumab	<ul style="list-style-type: none"> <li>• It uniquely binds to the CD147, thereby inhibits the binding of SARS-CoV-2 spike protein to the cell membrane.</li> <li>• A recent clinical trial conducted on COVID-19 (17) patients with meplazumab efficiently improved the recovery of patients with SARS-CoV-2 pneumonia. During the recovery phase, treated patients have shown normalized lymphocyte count without any side-effects [169].</li> </ul>
PD-1 antagonist	Camrelizumab	<ul style="list-style-type: none"> <li>• A monoclonal antibody against Programmed Cell Death Protein 1 (PD-1) and approved for the treatment of Hodgkin lymphoma [170].</li> </ul>
Antiviral peptide	CSA0001	<ul style="list-style-type: none"> <li>• Human cathelicidin LL-37 is a host defense peptide with immunomodulating properties against bacterial and viral infections [171].</li> </ul>
TLR agonists	PUL-042, Polyinosinic-polycytidylic acid (poly I:C)	<ul style="list-style-type: none"> <li>• PUL-042 is a TLR2/6/9 agonist.</li> <li>• Poly I:C is a TLR3 agonist.</li> </ul>
IL-6 antagonist	Siltuximab	<ul style="list-style-type: none"> <li>• Effective in reducing cytokine release syndrome (CRS) [172].</li> </ul>
IL-6 receptor antagonist	Sarilumab, Tocilizumab	<ul style="list-style-type: none"> <li>• Effective in reducing cytokine release syndrome (CRS) [172].</li> <li>• Use of tocilizumab in COVID-19 patients (n=30) shown reduced mechanical ventilation [173-175].</li> </ul>
GM-CSF antagonist	Gimsilumab, TJ003234	<ul style="list-style-type: none"> <li>• Monoclonal antibodies act as an antagonist to GM-CSF.</li> </ul>
Inhibition of SARS-CoV-2 induced inflammatory innate and adaptive immune responses	Intravenous immunoglobulin (IVIG)	<p>Suppresses the inflammatory responses mediated by hyperactivated innate and adaptive immune cells [176,177].</p>

Virus neutralization	Immunoglobulin from recovered patients, Anti-SARS-CoV-2 inactivated convalescent plasma	<ul style="list-style-type: none"> <li>• Passive immunization of seroconverted antibodies neutralizes the virus particles.</li> <li>• Treatment of COVID-19 patients with plasma that has been collected from the COVID-19 recovered patients has shown reduced viral load with improved clinical symptoms [178-180].</li> </ul>
Viral load clearance	NK cell treatment, NKG2D-ACE2 CAR-NK Cells	<ul style="list-style-type: none"> <li>• This strategy inhibits the surplus release of cytokines and neutralizes the GM-CSF, clear the virus-infected cells [67].</li> </ul>
<i>Non-specific immunosuppressors/immunomodulators</i>		
Cellular therapy	Mesenchymal stromal cells	<ul style="list-style-type: none"> <li>• These cells localize at the site of injury and especially inflammation at which they induce anti-inflammatory. Also, they modulate the function of active T cell to regulatory phenotype [181].</li> </ul>
Steroid drugs	Corticosteroids	<ul style="list-style-type: none"> <li>• Conflicting results have been reported from different treatment centers.</li> <li>• In addition, they develop diversified side effects, including the possibility of secondary infections, non-specific immunosuppression, deferred viral clearance impaired antigen-specific antibody responses, avascular necrosis, and osteoporosis [182,183].</li> </ul>
Anti-rheumatics	Leflunomide	<ul style="list-style-type: none"> <li>• Isoxazole derivative</li> <li>• It inhibits the dihydroorotate dehydrogenase by blocking the pyrimidine synthesis.</li> <li>• Making low availability of the pyrimidine pool, it affects the lymphocyte proliferation and inflammatory responses [184].</li> </ul>
Calcium channel blocker	Tetrandrine	<ul style="list-style-type: none"> <li>• Bisbenzylisoquinoline alkaloid.</li> <li>• It shows immunosuppressant activity by blocking calcium channels.</li> </ul>
Anti-parasitic drugs	Chloroquine/ Hydroxychloroquine, Ivermectin	<ul style="list-style-type: none"> <li>• Aminoquinolines derivatives mainly used for the treatment of malaria infections.</li> </ul>

		<ul style="list-style-type: none"> <li>• Despite their anti-malarial, anti-inflammatory, and immunomodulatory activity, anti-SARS-CoV-2 activity has also been reported in which CQ effectively binds to the sialic acids and gangliosides on the host cell surface thereby inhibiting the virus attachment. However, the later report is based on molecular modelling studies [185].</li> <li>• Besides, CQ/HCQ is active against COVID-19 when it is in combination with a macrolide antibiotic (azithromycin) but not alone [186-188].</li> <li>• Ivermectin exhibited in vitro anti-SARS-CoV-2 activity [189]. However, dose-escalation studies showed that a 'massive overdose' is required for antiviral activity in humans, which may raise further concerns about side-effects [190].</li> </ul>
Antibiotics	Azithromycin, Carrimycin	<ul style="list-style-type: none"> <li>• Macrolide antibiotics currently used against COVID-19 as an adjunct therapy.</li> </ul>

1203 Abbreviations: CQ/HCQ, (hydroxy)chloroquine; DAMP, Danger-associated molecular patterns;  
1204 GM-CSF, granulocyte-macrophage colony-stimulating factor; GvHD, graft versus host disease;  
1205 MS, multiple sclerosis; STAT, signal transducers and activators of transcription; VEGF, vascular  
1206 endothelial growth factor.

1207 \*The above-mentioned drugs are currently evaluated in clinical trials against COVID-19 (for  
1208 more information <https://clinicaltrials.gov/>).

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1211 Table 2. Expertise gained in the nanomedicine approaches for pulmonary infections.

Product/ Formulation type	Indication	Therapeutic observations	Comments
Lipoquin®	Local antibiotic treatment for lung infections	Ciprofloxacin unilamellar nano liposome nebulized delivery system provides the reduction of dose frequency to a once daily treatment while maintaining high local concentration in clinical evaluations compared to larger size liposomes [122].	Commercial nano liposomal products for lung delivery are intended to increase the permeation, intra cellular drug enhancement for pulmonary infections, and these approaches provide insights for the future therapeutics targeting systems with enhanced therapeutic response to fight pulmonary infections.
Arikayce® (liposomal Amikacin)	Nontuberculous Mycobacterial Lung Disease	Liposomal Amikacin system is shown to increase intracellular drug concentration and overall therapeutic improvement [123,191].	
Ambisome® (liposomal amphotericin B)	Allergic bronchopulmonary aspergillosis	Currently in phase 2 clinical trials for Allergic Bronchopulmonary Aspergillosis treatment (ClinicalTrials.gov Identifier: NCT02273661).	
Liposomal amikacin for inhalation (LAI)	Bronchiectasis (Phase II clinical trial)	LAI produces improvement in sputum conversion with limited systemic toxicity in patients with refractory MAC (Mycobacterium avium complex) disease [124].	Strategies with liposomal based nano or emulsified systems had high lung mucosa penetration capabilities. These strategies help in drug deposition with high retention in airways; these investigations provide clues for future COVID-19 like pulmonary infection associated drug delivery applications.
Tobramycin nano lipid carriers (NLCs)	<i>P. aeruginosa</i> infections associated with cystic fibrosis	Drug NLCs combat <i>P. aeruginosa</i> infection and also increase <i>in vivo</i> mucus penetration [192].	
pGM169 drug with GL67A lipid solution	Cystic fibrosis (Phase IIb clinical trial)	Increased drug deposition and retention in the proximal airways [193].	
MERS-CoV S-containing nanoparticles	Recombinant MERS-CoV S nanoparticle vaccine and Matrix-M1 adjuvant combination as a vaccine	MERS-CoV S nanoparticle vaccine produced high titter anti-S neutralizing antibody and protected mice from MERS-CoV infection <i>in vivo</i> [125].	Introduction of vaccinated with MERS-CoV S nanoparticles developed a MERS-CoV neutralizing antibody response targeted to the MERS-CoV S.

Immunoprophylactic strategy with protein cage nanoparticle (PCN)	Pulmonary viral infections including influenza viruses, a mouse-adapted SARS-coronavirus	Pulmonary instillation of PCN dramatically enhanced the subsequent host immune responses to primary viral infections of the lungs [126].	Like liposomal strategies, polymeric nano systems also enhance the localization of drug in the lung regions for a better therapeutic response.
PS-341 loaded PLGA-PEG NPs	Cystic fibrosis (Preclinical study in mice)	Enhanced drug localization with NPs to the lungs, helps in reducing immunosuppressive side effects resulting from PS-341 systemic administration over 11 days [127].	
PRINT® (Particle Replication in Non-wetting Templates) technology	Influenza vaccine	To deliver influenza vaccine antigens poly (lactide-co-glycolide) PRINT particles were designed to bind to a commercial trivalent injectable influenza vaccine electrostatically. [194].	Increased understanding of the delivery of the vaccine antigen. This approach has increased vaccine effectiveness and reduces the amount of antigen necessary to induce an immune response.
Gold nanorod-based heptad repeat (HR1) peptide inhibitor	Middle East respiratory syndrome coronavirus (MERS-CoV)	Pregnancy-induced hypertension (PIH), is a potent HR1 inhibitor and can selectively inhibit MERS-CoV S with an IC <sub>50</sub> value of 1.171 μM. The developed pregnancy-induced hypertension (PIH) gold nanorods (PIH-AuNRs) exhibit a 10-fold higher inhibitory activity than PIH and can completely inhibit cell fusion at 1.171 μM with good biostability, excellent targeting ability and minimum off target effects. Therefore, PIH-AuNRs are a promising antiviral agent and may have a huge impact on developing pharmaceuticals in the clinic [119].	HR1 peptide inhibitors have been developed to inhibit HR1/HR2-mediated membrane fusion between MERS-CoV and host cells, which is the major pathway of MERS-CoV-induced host infections.
Virus like nanoparticles (VLPs)	In enhancing or triggering the strong immune response in pulmonary	Virus mimicking empty particulate structures [128,129].	Hollow virus like particulate structures which lack in genetic material will provoke or enhance a strong immune response to combat

	infections		lung associated infections.
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1214 **Boxes**

1215 **Box 1: Lung physiology.**

1216           Bronchi start from the trachea and extend to all parts of the lungs via bronchioles. The  
1217 lung epithelium is comprised of different columns, which consist of mucus-secreting goblet cells,  
1218 mucus clearance microvilli ciliated cells and cuboidal cells. The alveolar epithelium forms a tight  
1219 barrier and regulates the movement of fluid and proteins from the circulatory system to the  
1220 airspaces, and it regulates the entry of pathogenic substance that comes during the inhalation  
1221 process. The alveolar epithelium contains two types of cells, alveolar type I (principal  
1222 component) and II cells. Both cell types form a lining to the endothelial basement membrane and  
1223 primarily type 1 cell perform diverse functions, including barrier function, fluid reabsorption, gas  
1224 exchange function, and others.

1225           Nevertheless, type I cells are more susceptible to infections, injury, and cell death. Type  
1226 II cells (pneumocytes) produce surfactants, which exist in the alveolar lining reduce the liquid  
1227 surface area/surface tension [195]. Type II cells also act as the progenitor for type I cells during  
1228 injury. This integrity of these two epithelial cells is maintained by the transmembrane proteins,  
1229 such as claudins, occludins, and others.

1230           Gas ( $O_2/CO_2$ ) transport and exchange is the primary function of lungs in the human body.  
1231 In physiological conditions, the lungs exhibit excellent elastic characteristics of the lung  
1232 parenchyma and surface tension of alveoli. The elastic properties are acquired by the  
1233 components, such as elastic fibers (elastin, microfibrils), fibril forming collagens (tensile  
1234 strength, type I, II, III, V, XI), and geometric arrangement.

1235           In general, during the infections, the lung epithelium senses the pathogens and/or injury  
1236 and produce pro-inflammatory cytokines, chemokines, and other danger signals, which will  
1237 recruit leukocytes [195]. Recruited antigen-presenting cells (APCs) also recognize the invading  
1238 pathogens, and pathogen-associated molecular patterns (PAMP) by pattern recognition receptors  
1239 (PRRs) followed by the activation of innate immunity system and recruitment of innate immune  
1240 cells, which can clear the pathogen via phagocytosis processes. Further, the activated innate  
1241 immune system helps in the development of adaptive immune responses (both effector and  
1242 memory) against a pathogen [32].

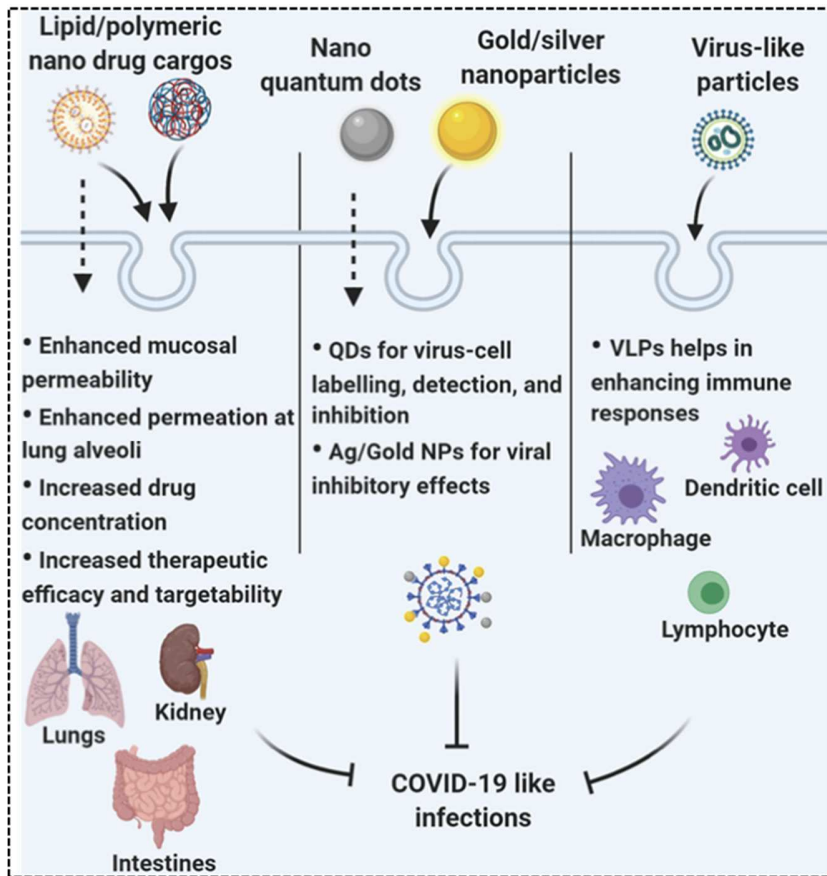
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1244 **Box 2: Key observations that need to be considered for designing the COVID-19**  
1245 **therapeutics**

- 1246 • The RNA of the virus is protected by a lipid layer/envelope that allows the virus to  
1247 penetrate the cells of the ocular, nasal, and buccal mucosa.
- 1248 • Spike proteins are responsible for the entry of the virus.
- 1249 • Unlike other CoVs, SARS-CoV-2 has a slight difference in their temperature  
1250 withstanding capacity, humidity and type of material where it lies.
- 1251 • Observational studies of ABO blood groups on large population confirmed that Rh  
1252 (called Rhesus factor) positive and Rh/ABO blood group is positively and significantly  
1253 correlating to intubation and death [196]. Likely, the O blood group has a lower risk of  
1254 infection compared to other blood groups and the B blood group has a higher risk of  
1255 infection [196,197]. However, earlier studies on SARS-CoV-1 has shown the contrary  
1256 results [198].
- 1257 • Although reasons are not known, children are likely to be resistant to SARS-CoV-2  
1258 infection and developing severe disease [199,200]. One of the plausible reasons is the  
1259 existence of rapid producing, broad reactive and variable affinity natural antibodies  
1260 [201].
- 1261 • Pre-existing cross reactive T and B cells (including antibodies) against SARS-CoV-2  
1262 have been observed in unexposed healthy donors [202-208]. Probably, this contributes a  
1263 clue to develop tailor-made, cross-protective vaccines against SARS-CoVs.
- 1264 • Age, gender and underlying chronic diseases have played a significant role in mortality  
1265 by COVID-19.
- 1266 • Although the S protein is the best target for vaccine development, nucleic acid-based  
1267 vaccines should not be undermined.
- 1268 • M protein in all CoV exhibits N-terminal ectodomain glycosylation site. However, once  
1269 glycosylated, M protein becomes inactive. Therefore, enhancing the glycosylation is a  
1270 possible intervention strategy [209].
- 1271 • It is still premature to confirm the effect of COVID-19 on diseases such as diabetes,  
1272 hypertension, cardiovascular disease, cancer, inflammatory bowel disease, and others.

- 1273       • Substantial data are yet be obtained on the effects of COVID-19 in the patients who are  
1274       under immunosuppressive and/or anti-inflammatory/disease-modifying antirheumatic  
1275       drugs.



**Nanomedicine Therapeutic Strategies for COVID-19 Like Infections**